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(54) Title: LOCALLY ADMINISTRABLE, BIODEGRADABLE AND SUSTAINED-RELEASE PHARMACEUTICAL COMPOSITION FOR PERIODONTITIS AND PROCESS FOR PREPARATION THEREOF																	
<p style="text-align: center;">Plaque Indices</p> <table border="1"> <caption>Plaque Index Data (Estimated from Graph)</caption> <thead> <tr> <th>Weeks</th> <th>Control</th> <th>Exp.</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>3.0</td> <td>3.0</td> </tr> <tr> <td>1</td> <td>2.8*</td> <td>2.7*#</td> </tr> <tr> <td>2</td> <td>2.4*</td> <td>1.5*#</td> </tr> <tr> <td>4</td> <td>1.6*</td> <td>1.3*#</td> </tr> </tbody> </table> <p>* ; significantly different from baseline (0 week) # ; significantly different from control group</p>			Weeks	Control	Exp.	0	3.0	3.0	1	2.8*	2.7*#	2	2.4*	1.5*#	4	1.6*	1.3*#
Weeks	Control	Exp.															
0	3.0	3.0															
1	2.8*	2.7*#															
2	2.4*	1.5*#															
4	1.6*	1.3*#															
(57) Abstract <p>This invention relates to locally administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis and process for preparation thereof, which can show continuous drug effect for a long time by controlling the release time and by making drug remain in the periodontal pocket for prolonged time wherein they are prepared by i) making the microsphere containing the physiologically active substance, ii) making the mixture of the microspheres and water-soluble polymer such as polysaccharides, iii) making the mixture into the form of film or strip or/and iv) coating the film or strip with cation aqueous solution such as calcium and barium. The present pharmaceutical composition can be easily administered using forceps, minimized side effect and maximized the effect by releasing the active substance at the minimum dose, and make the patients feel comfortable.</p>																	

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Title of Invention

Locally administrable, biodegradable and
sustained-release pharmaceutical composition for
5 periodontitis and process for preparation thereof

Background of the Invention

This invention relates to locally
10 administrable, biodegradable and sustained-release
pharmaceutical compositions for periodontitis, and
its process for preparation thereof, which can show
continuous drug effect for a long time by controlling
the release time and by making drug remain in the
15 periodontal pocket for prolonged time wherein they are
prepared by i) making the microsphere containing the
physiologically active substance, ii) making the
mixture of the microspheres and water-soluble polymer
such as polysaccharides iii) making the mixture into
20 the form of film or strip or/and iv) coating the film
or strip with aqueous solution of cation such as
calcium and barium chlorides.

Periodontitis is an inflammation of the teeth
supporting tissue caused by bacterial toxin, which is
25 an metabolizing product of oral bacteria. If

periodontitis in the initial stage that is gingivitis is not treated properly, it will develop into severe periodontitis with swelling gingiva, bleeding and bad breath. If periodontitis goes on, the collagen supporting the periodontal membrane is destroyed, and alveolar bone under the teeth is resolved. As a result, periodontal ligament is separated, and periodontal pocket is formed, and in severe case, it will develop into advanced periodontal disease which can lead to loss of teeth. Most of the germs causing periodontitis are anaerobic gram-negative bacteria, and they secrete collagenase which destroy ligament that is connective tissue of the periodontal membrane, and metabolite from above reaction cause periodontitis.

For prevention and treatment of the advanced periodontal disease, removal of the plaque in the periodontal pocket is essential. The methods for removal of the bacterial plaque can be divided into apparatotherapy and chemotherapy. Apparatotherapies include scaling and root planing, and require the patient's ability to control plaque continuously, but have disadvantage that apparatotherapies have a limited effect on the part at which it is difficult to brush teeth due to anatomical reason. For supplement of the above disadvantage of apparatotherapies, the plaque

control using chemotherapies has been studied and it is reported that chemotherapies are very effective on the removal of bacteria which live in the deep part where instruments are difficult to reach.

5 The most important thing in the clinical use is to retain the effective concentration of the active substance which control plaque in the bacterial invasion site for a long time without side-effect. The examples of chemical method include irrigating the
10 invaded region with an antibiotic solution, and administering antibiotics systemically. It is known that local administration of antibiotics has a limited effect on the removal of the bacteria causing periodontal disease because antibiotics cannot reach
15 deep part of subgingival area or cannot last for enough time. It is reported that the systemic administration is effective on the treatment for the periodontal disease, but in the case of the systemic administration in order to maintain the effective
20 concentration at the infected region it is required that large dosage of medicine is administered and subsequently side effects result, for example, the appearance of resistant bacteria and undesired action to intestinal bacteria. Therefore, to overcome this
25 defect, the research for the direct administration into

the periodontal pocket has been conducted, and it is reported that if tetracycline is administrated locally, only 1/1000 dosage of the systemic administration can bring the same effect (Goodson, J. M. et al., *J. Periodontol*, 56 265-272, 1985).

In order to bring the maximum effect and minimum side-effect, it has been attempted to develop the local drug delivery system using the controlled release system of physiologically active substance such as antibiotics.

There are a few of problems that must be solved to treat the periodontitis by local drug delivery system.

First, a carrier is necessary to transport a physiologically active substance such as antibiotics to the periodontal pocket. A large number of carriers developed so far are substances not absorbed biologically, which must be removed after drug is released completely and if not, they irritate the periodontal tissue and inhibit the regeneration of the periodontal tissue.

According to USP 5,599,553, it is reported

that a pharmaceutical preparation composed of minocycline HCl and polycaprolactone in the form of strip can release the active substance for 7 days in the periodontal pocket. In this case polycaprolactone
5 must be removed after drug is released completely because it takes too long time to be decomposed in the body.

Second, to treat the periodontitis, effective concentration of the active substance in the
10 periodontal pocket must be maintained for a long time. It is reported that to treat the periodontitis the effective concentration of antibiotics such as minocycline HCl must be maintained for at least 7 to 10 days (Lawter J. R. et al., *Int. sym. cont. Rel, Bioact.*
15 *Mater.*, 230-31, 1990). It is reported that the therapeutic agent should be retained as long as possible because dental disease is generally chronic (Friedman M. et al., *Pharmaceutical Research*, Vol. 7, No. 4, 313 - 317, 1990). In addition, it is known
20 that, if administered orally, administration for more than two weeks is effective for the treatment for periodontitis (Lilijenberg B et al., *J. Clin. periodontol.*, 7, 48-61, 1980).

According to USP 4,933,182, a pharmaceutical
25 preparation wherein polymeric microparticles containing

one or more substances is dispersed into the continuous phase of water soluble polymer has a advantage that it can release substance in independent pattern and it does not give unpleasant feeling to the patients, but
5 it has disadvantage that administration should be made often because the release of substance is completed in about 6 hours.

Third, it is needed that the process of administration is convenient and quantitative on the
10 basis of the amount of active substance.

According to USP 4,175,326, a pharmaceutical preparation containing the active substance in hollow fiber device made up of cellulose acetate is reported. In order to administer this preparation into the
15 periodontal pocket, fiber should be cut into the length for the dosage, and then the cut fiber must be coiled around the teeth, and then it must be administrated in the way of pushing it into the periodontal pocket. This method has disadvantage that it is inconvenient to
20 administer drug into the periodontal pocket quantitatively.

According to WO A1 92/07555 and USP 5,324,520, a in situ gel has been reported which is in a liquid state before administration and becomes a little
25 hardened state after administration. Because the

formulations are in a liquid state before administration, special administering tool is needed in the form of syringe and these formulations also have disadvantage that it is inconvenient to administer quantitatively.

In order to satisfy the most important things for treating the periodontitis, that is to say, biodegradation and continuous drug release, microspheres made up of biodegradable polymer has been prevailed which is dissolved when it is administered into the periodontal pocket and release drug continuously. For example, it is reported that they suspended PLGA microspheres including tetracycline in Pluronic® F 127 gel and then inserted the prepared formulation in the peridontal pocket (EP A1 244118). In addition, it is reported that they can maintain the effective concentration in the periodontal pocket for 14 days by inserting microsphere containing minocycline and PLGA (Lawter J. R. et al., *Int. Symp. Cont. Rel. Bioact. Mater.*, 230 - 231, 1990), and filed a patent application therefor. The formulation for treating periodontitis using such biodegradable microspheres can retain the effective drug concentration in the periodontal pocket for a long time by single dose, and the feeling of foreign substance does not exist because

the formulation was prepared by microparticle, and there is no need to remove after treatment because the formulation is biodegradable. However, since microspheres prepared in the form of gel can not last
5 for a long time due to its hydrolytic property, there is inconvenience that it should be prepared just before use, and that special administering tool is needed in order to insert gel into the periodontal pocket. And it is difficult to administer quantitatively and
10 accurately when we insert the microspheres directly into the periodontal pocket.

Therefore, in order to develop ideal formulations for periodontitis, it is desirable that biodegradable substance is used to control drug
15 release, the effective drug concentration is maintained continuously and the administration is convenient for patients.

The present inventors have been conducted the continuous study for the ideal formulation for
20 periodontitis, and we found that if the biodegradable microspheres containing physiologically active substance for periodontitis is mixed with the hydrogel of water soluble polymer and then the mixture is made into the form of thin film or strip, and this film or
25 strip is insterted into the periodontal pocket, it will

show the continuous effect for a long time, since water soluble polymer is decomposed slowly, on contacting saliva and the gingival crevice fluid, and subsequently only the microspheres became left alone in the periodontal pocket and these microspheres release the active substance continuously. In addition, the inventors discovered that when the film or strip is spray-coated with aqueous solution of cation salt such as Ca^{2+} or Ba^{2+} , disintegration time can be controlled effectively.

Summary of the Invention

The present invention relates to the locally administrable, biodegradable, and sustained-release pharmaceutical compositions and process for preparation thereof.

More specifically, the present invention provides composition in the form of thin film or strip composed of microspheres made with biodegradable polymer and water-soluble polymer such as polysaccharides.

And the present invention provides composition composed of the above thin film or strip coated with cation salt aqueous solution.

In addition, the present invention provides process for preparing composition comprising the steps, 1) making the biodegradable microspheres containing the biologically active substance, 2) 5 mixing the microsphere and water-soluble polymer such as polysaccharides, 3) making the mixture into the form of thin film or strip. The present invention provides process for preparing composition comprising the step of coating the film or strip with metal cation aqueous 10 solution in addition to the above-mentioned process.

Brief Description of The Drawings

15 In the accompanying figures:

Fig. 1 is indices of plaque comparing control group with those of experimental group;

20 Fig. 2 is indices of gingiva comparing control group with those of experimental group;

Fig. 3 is pocket depth comparing control group with those of experimental group;

Fig. 4 is indices of bleeding comparing control group with those of experimental group;

25 Fig. 5 represents the variation of ratio of

cocci, non-motile rod, motile rod and spirochete in the control group;

Fig. 6 represents the variation of ratio of cocci, non-motile rod, motile rod and spirochete in the experimental group;

Fig. 7 is CFU of black-pigmented bacteroides in control vs experimental group;

Fig. 8 is CFU in control vs experimental group cultured on aerobic blood agar plate;

Fig. 9 is CFU in control vs experimental group cultured on anaerobic blood agar plate;

Detailed Description of the Invention

15

Physiologically active substance of the present invention which can be used for treating periodontitis contains antibiotics, local anesthetics, antiinflammatory analgesics, and steroid hormones.

20 Antibiotics which can be used in the present invention contain ampicillin, amoxicillin, erythromycin, tetracycline, minocycline, oxytetracycline, doxycycline, metronidazole, bacitracin, kitasamycin, spiramycin, ornidazole, and salt thereof, which are
25 used generally to treat periodontitis, and local

anesthetics which can be used in the present invention contain lidocaine, procaine, dibucaine, and benzocaine, antiinflammatory analgesics which can be used in the present invention contain diclofenac, flubiprofen, 5 ibuprofen, ketoprofen, aspirin, mefenamic acid and acetaminophen, and steroid hormones which can be used in the present invention contain dexamethasone, triamcinolone acetonide, hydrocortisone and epihydrocortisone.

10 Biodegradable polymer used in preparing for microsphere of the present invention is polymer of the derivatives of α -hydroxy-carboxylic acid, for example, polymer of glycolic acid(PGA), polymer of lactic acid(PLA), and copolymer of lactic acid and glycolic 15 acid(PLGA) which can be hydrolyzed into water and carbon dioxide which are not harmful to human body.

The molecular weight of these polymers have an important effect on the period of drug release and degradation of the microspheres.

20 When we use a polymer group of PLA, PGA and PLGA, the more the molecular weight increases, the longer the drug release time as well as degradation of the polymers occurs. The release time and degradation of the polymers is postponed when the ratio of lactic 25 acid increased in the use of PLGA copolymer.

If we make use of this property, we can control the releasing time of microspheres. Therefore when the releasing time is determined as two weeks to treat periodontitis, the desirable range of molecular weight is 4,000 to 50,000, and the more desirable range is 5,000 to 15,000. In order to administer the various kinds of drug simultaneously, we can make microspheres using polymers of different molecular weight, and each microspheres will show the independent release pattern.

10

The inventors invented a pharmaceutical composition in the form of film or strip made up of the mixture of the microspheres and water-soluble polymer hydrogel in order to administer an active substance quantitatively into the periodontal pocket. In other words, if the microspheres can be maintained in their original form in the film or strip made up of the mixture of microspheres and water-soluble polymer, the quantity of the microsphere in the film or strip can be calculated and quantity of administered drug into the periodontal pocket can be determined by the mixture ratio of the microspheres and water-soluble polymer, and quantitative administration can be possible.

15
20

25 The desirable water-soluble polymer used in

pharmaceutical composition of the present invention should be harmless to human body and viscous in the aqueous solution, and easy to be formed into the film or strip after drying. These contain the
5 polysaccharides such as pectin, carrageenan, gelatin, sodium alginate or chitosan.

In the present invention, if we coat the above-mentioned film or strip with the aqueous solution
10 of cation such as calcium and barium, it is possible to delay the disintegrating time.

That is, if film or strip without coating is administered into the periodontal pocket, it swells so fast on contacting with saliva or gingival crevice
15 fluid that a part of the film or strip can be out of the periodontal pocket, and there is a large opportunity to lose the part of the film or strip, and to decrease the amount of an active substance in the periodontal pocket, and we can not have an desirable
20 treatment effect, because the dosage is practically diminished than the amount delivered to the periodontal pocket. To solve this problem, the present inventors invented the pharmaceutical composition using a complex of the polysaccharides and metal ion.

25 When water-soluble polymer such as

polysaccharides forms complex with the metal ion, its solubility to the water decreases and the rate of the swelling gets slow. Therefore, in the early stage of the administration, the possibility of the loss of the film or strip disappears, and administered drug remains
5 in the periodontal pocket more safely.

Since the solubility to the water and swelling rate of the complex make up of the polysaccharides and metal depend on the kinds of the metal cation, we can
10 choose proper metal ion considering the treatment period, etc.

The desirable cation salt may contain cation chlorides, such as calcium chloride, magnesium chloride, barium chloride, and aluminum chloride.

15 Especially calcium chloride is suitable to the formulation which is hydrated by saliva or gingival crevice fluid in the short time, 3 to 6 hrs, and barium chloride is suitable to the pharmaceutical formulation for longer time, one week to two weeks.

20 It is possible to make film or strip coated with cation aqueous solution utilizing a simple step such as spray-coating when we use polysaccharides.

It is found that different formulation has own disintegration time. The formulation which is not
25 combined with metal ion maintains its original shape in

the periodontal pocket only for two hours,
calcium-polysaccharides for 3 to 6 hrs, and
barium-polysaccharides for more than one week. When
the formulation is disintegrated, only the microspheres
5 remain in the periodontal pocket, and release an
active substance continuously.

Therefore, in the present invention it is possible to
administer an active substance into the periodontal
pocket quantitatively by using film or strip made up of
10 polysaccharides and microspheres, and it is possible to
control the maintenance of the film or strip in the
periodontal pocket by controlling the disintegration
time by coating the film or strip with aqueous solution
of cation salt.

15

The followings explain the process for
preparing the locally administrable, biodegradable and
sustained-release pharmaceutical composition for
periodontitis,

20 1) the step for making microspheres, by
dissolving a biodegradable polymer such as PLA or PLGA
in the methylene chloride, by suspending a finely-
powdered active substance, and by emulsifying the
suspended solution in the aqueous solution containing
25 the surfactant,

2) the step for making hydrogel, by mixing microspheres and polysaccharides and by adding distilled water,

3) the step for foming into film or strip.

5

In addition, another process for preparing locally administrable, biodegradable and sustained-release pharmaceutical composition includes step

10 4) for coating the film or strip with aqueous solution of cation salt in addition to the above-mentioned step 1), step 2), and step 3).

The process for preparing the locally
15 administrable, biodegradable pharmaceutical composition for periodontitis will be explained by steps in detail in the followings.

I. Step 1

20 The microspheres used in the present invention is prepared by the process which is applied for patent by the present inventors (Korean patent No. 95-10671), and on which the priority of the present invention is based.

25 Microspheres which contains more than 20 weight % of

an active substance and release the active substance at the effective concentration and within 2 weeks are made as the followings.

5 First of all, in the case that an active substance is water-soluble, we crushed the substance into the average diameter below $5\mu\text{m}$ by using Jet-mill. In the case of organic-soluble substances, this process is not necessary.

10 We mixed biodegradable polymer, PLA or PLGA, with the active substance in the proper ratio. Addition of methylene chloride into it, the mixutre is mixed well, followed by cool down below 20°C .

15 After emulsifying the polymer solution by addition to aqueous polyvinyl alcohol which precooled below 5°C , the emulsion is diluted with distilled water. Finally, methylene chloried is evaporated to achieve our goal which mentioned above. When we made microspheres according to the above method using D,
20 L-PLA whose molecular weight is 6,500 to 8,000, the release of active substance was completed within 2 weeks.

 When we used PLGA whose molecular weight is 8,000 to 10,000 the release of substance was
25 accomplished within 2 weeks also. The desirable amount

of active substance contained in the microspheres is about 10 to 30 weight %. Especially 20 to 25 weight % is more desirable.

In addition, the particle size of microspheres have important effect on the drug content and the rate of the drug release. The average particle size which can be used is 1 to 500 μ m, and 10 to 200 μ m is desirable, and 20 to 150 μ m is more desirable.

It is desirable that the microspheres release the active substance continuously for more than 7 days and less than 20 days.

II. Step 2

The process for mixing polysaccharide and microspheres will be explained in the followings.

First of all, we mixed sustained-release microspheres containing the active substance and polysaccharides. At this time the mixing ratio is the important factor not only on the administration volume of the formulation, but also on the extent of loss of microspheres from the periodontal pocket due to increased volume as polysaccharide is swollen. Therefore, it is desirable to use polysaccharide as little as possible, and it is desirable that the ratio of polysaccharide to the total mixed pharmaceutical

composition is 5 to 50 weight %, and more desirable is 5 to 30 weight %.

Then we added distilled water to the above mixture and made hydrogel of polysaccharide in which microspheres are suspended. The concentration of polysaccharide, that is, the quantity of the added distilled water is very important factor, when we make film or strip. If the quantity of the added distilled water is too large, it is difficult to form film or strip, and if the quantity of the added distilled water is too small, it is difficult to make film or strip containing an active substance homogeneously because it is difficult to disperse microspheres in the hydrogel evenly. Thus, considering the above factors, it is desirable to add the distilled water enough to make hydrogel which contains polysaccharide below 50 weight %, and it is more desirable to make hydrogel which contains polysaccharide at the ratio of 1 to 20 weight %.

20

III. Step 3

In order to insert the above hydrogel into the periodontal pocket, it is formed into the film or strip as the followings.

25

First, hydrogel is put and flattened on the

acryl board or metal board, and then covered with the polyester film coated with silicon, and compressed with roller to make in even the thickness, and then polyester film is removed, and dried in the air. The resultant film is cut into the proper size to insert it into periodontal pocket. We can make strip by another method wherein the above water-soluble polymer hydrogel is put in the frame and compressed. On making film or strip, we determine the thickness of the film or strip considering the size of the periodontal pocket. The desirable thickness of the film or strip is below 2mm, and the more desirable thickness is 0.1 to 1.0mm. The desirable example of the pharmaceutical composition is 6mm¹02mm in width and 0.1 to 2mm in thickness are wedge type in the shape.

IV. Step 4

To increase the maintenance of the formulation in the periodontal pocket, it is desirable to decrease the viscosity after hydration and to the disintegration time by coating film or strip with aqueous solution of cation salt. The desirable cation salt contains calcium chloride, magnesium chloride, barium chloride and aluminum chloride, and especially calcium chloride is suitable to the pharmaceutical composition of the

present invention which is hydrated by saliva or gingival crevice fluid in 3 to 6 hrs, and barium chloride is suitable to the compositions which can be maintained for 1 to 2 weeks.

5 The desirable concentration of 2(II) or 3(III) cation aqueous solution is 1 to 10%, and 2 to 5% is more desirable.

 There are two kinds of coating methods. One is to coat film or strip by soaking it in aqueous
10 solution of cation and the other is to coat the film or strip by spraying the aqueous solution of cation.
The latter is more desirable.

 The pharmaceutical composition for
15 periodontitis of the present invention is inserted into the periodontal pocket, and polysaccharide is hydrated by saliva and dissolved, and only the biodegradable microspheres remain in the periodontal pocket and release the active substance for 1 to 2
20 weeks.

 Because the present invention is for local administration, we formulate with the minimum dosage for the periodontal pocket. Consequently it can be minimized the side effect which can be accompanied when
25 it is administered excess amount for extended time.

And because the pharmaceutical composition contains sustained-release microsphere, administering effect of single dose can last for two weeks. In addition, because the form of pharmaceutical composition is film or strip, we can administer the drug with forceps conveniently, and because the composition consists of biodegradable substance, there is no need to remove the remnant after the release of an active substance is completed.

And by coating the drug with 2(II) cation chloride aqueous solution, the pharmaceutical composition of the present invention can remain in the periodontal pocket more safely.

Therefore, it has great advantage that we can maximize the drug release effect and the usage is very convenient. The present invention will be explained in more detail by examples.

The following examples are only for showing the application of the present invention, but the claims of the present invention is not limited within these examples.

Preparation example 1: The preparation of the biodegradable microsphere containing antibiotics

Minocycline loaded microspheres were prepared by a modified O/W emulsion technique. A 0.6 g of micronized minocycline HCl (particle size was below 5 μ m) was added to 2ml methylene chloride containing 1.4 g polylactic acid of molecular weight 7,500. The resultant suspension was poured into a beaker containing 200ml of 5% polyvinyl alcohol aqueous solution at 5°C that was being mechanically stirred. Stirring continued for 1 hr to permit evaporation of the solvent. The microspheres were collected, washed with water, and lyophilized using a freeze-dryer. The average particle size was 100 μ m and the drug content was 24 weight %.

Preparation example 2 to preparation example 7

We prepared microspheres by the same method as described in preparation example 1 using various polymers and active substances. Table 1 shows their particle size and content of the active substances.

<Table 1> Microspheres containing active substance.

		polymer (average molecular weight)	active substance	Average size (μm)	drug content (weight %)
5	preparation example 2	PLA(8,000)	Minocycline HCl	120	22
	preparation example 3	PLA(10,000)	Tetracycline HCl	75	20
	preparation example 4	PLGA(8,500)	Minocycline HCl	100	23
	preparation example 5	PLA(14,000)	Metronidazole	110	25
	10	preparation example 6	PLGA(8,500)	Flubiprofen	100
preparation example 7		PLA(7,500)	Dibucaine	120	21

**Example 1 : The preparation of the pectin film
containing microspheres**

After we mixed 0.8g of microsphere prepared in preparation example 1 and 0.2g of pectin, 2.0g of distilled water is added to the mixture to obtain the hydrogel containing microspheres.

The above hydrogel is put and flattened into the acrylic mold box whose width is 10cm¹010cm, and whose thickness is 0.5 mm, and whose bottom is closed. And we covered it polyester film coated with silicon, and compressed it by roller, and removed the polyester film and dried at the room temperature. The resultant

film is cut in the size of 6mm¹02mm.

Example 2 : The preparation of pectin strip containing microspheres.

5 After we prepared hydrogel containing microspheres by the same method as described in example 1 we put it into the wedge type mold whose width is 6mm, and whose length is 2mm and whose depth is 0.1mm to 0.5mm. And covered polyester film coated
10 with silicon, and compressed it by roller, and removed the polyester film, and dried it at the room temperature, and separated strip from the mold.

Example 3 : The preparation of the sodium alginate film containing microspheres

15 After we mixed a 0.1g of sodium alginate and 0.85g of microsphere of the above preparation example 2, we added 1.5g of distilled water to the mixture to obtain the hydrogel containing microspheres.. We
20 prepared film with hydrogel by using the same method as described in example 1.

Example 4 : The preparation of the calcium alginate film containing microspheres

25 The calcium alginate film is prepared by

spraying 2% calcium chloride aqueous solution to the sodium alginate film prepared in Example 3 and drying it.

5 **Example 5 to Example 16**

 The strip or film was prepared by the same method as described in example 1 to 4 by using microspheres which was prepared by the same method as described in preparation example 2 to example 7. The
10 result is shown in table 2.

<Table 2> The film or strip containing microspheres

	Microsphere	Polysaccharides	Microspheres/ Polysaccharides	Shape	Coating
Example 5	Preparation Example 2	sodium alginate	80/20	Strip	-
Example 6	Preparation Example 3	sodium alginate	85/15	Strip	Calcium Chloride
Example 7	Preparation Example 3	sodium alginate	85/15	Strip	Barium Chloride
Example 8	Preparation Example 4	pectin	90/10	Film	Calcium Chloride
Example 9	Preparation Example 4	pectin	90/10	Film	Barium Chloride
Example 10	Preparation Example 5	carrageenan	90/10	Film	Calcium Chloride
Example 11	Preparation Example 3	carrageenan	80/20	Film	Barium Chloride
Example 12	Preparation Example 4	carrageenan	80/20	Strip	-
Example 13	Preparation Example 4	gelan	80/20	Strip	-
Example 14	Preparation Example 6	gelan	70/30	Film	Calcium Chloride
Example 15	Preparation Example 6	gelan	80/20	Film	Barium Chloride
Example 16	Preparation Example 7	gelan	75/25	Film	Barium Chloride

Test 1 : In vitro release test.

Films or strips of above examples were tested in 10ml of 10mM phosphate buffer pH 7.4 at 37°C in a shaking water bath. The amount of released drug was
 5 analyzed by measuring the UV absorbance according to the time. Table 3 shows the results.

<Table 3> Drug release Test

10

Hour(Day)		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
The Cumulating Releasing Quantity	Example 1	20	30	39	47	55	61	69	77	84	90	94	97	99	100	-	-
	Example 3	18	25	33	42	48	56	63	70	76	80	85	89	93	95	97	99
	Example 4	19	26	34	43	49	57	64	70	76	81	86	89	93	95	98	100
	Example 6	22	28	34	40	46	52	59	65	71	77	83	88	92	95	97	99
	Example 7	21	27	33	39	45	51	57	63	69	75	80	85	90	94	97	99
	Example 8	16	25	34	42	50	58	66	74	81	88	94	98	100	-	-	-
	Example 11	22	28	34	40	46	52	58	64	70	76	82	87	91	94	97	100
	Example 12	17	26	35	43	51	58	66	74	80	87	93	97	100	-	-	-
	Example 13	18	28	34	42	50	58	66	74	80	87	93	97	100	-	-	-
	Example 14	20	28	36	44	52	60	67	75	82	89	96	99	100	-	-	-
	Example 15	20	28	36	44	52	60	67	75	82	89	96	99	100	-	-	-
	Example 16	21	28	36	44	52	60	67	75	82	89	94	97	99	100	-	-

Test 2 : Disintegration test of the pharmaceutical composition

Among the above examples, we added the drug prepared by sodium alginate or pectin, and the drug coated with calcium chloride aqueous solution on this drug, and the drug coated with barium chloride aqueous solution on this drug to the pH 7.4 phosphate buffer solution at 37°C, and measured the time on which the formulation disintegrated completely. The result is on table 4.

<Table 4> The Result of dissolution test of the drug.

Sample	Polysaccharides	Coating	Time necessary for the dissolution of the drug
Example 3	sodium alginate	-	1 hr
Example 6	sodium alginate	Ca ²⁺	4 hr
Example 7	sodium alginate	Ba ²⁺	11 days
Example 1	pectin	-	1.5 hr
Example 8	pectin	Ca ²⁺	5 hr
Example 9	pectin	Ba ²⁺	12 days

Test 3 : Drug effect test administrated to the animal

This test was conducted in order to confirm a physiological effect of the pharmaceutical composition for the periodontitis (composition composed of sodium alginate and polylactic acid microspheres containing minocycline) prepared by the method described in Example 3.

The above formulations (film cut by 6x2 mm) were administered to the periodontal pockets of dogs, and after 0, 1, 2, and 4 weeks, each clinical index was measured. The morphology of bacteria was measured with
5 a microscope, and the colony number of bacteria by cultivation was measured.

And the data like this was analyzed statistically by ANOVA method in order to confirm the significant
10 difference between before administration and after administration.

The clinical indices such as plaque indices, gingival indices, and bleeding indices were measured
15 by Loe & Silness method, and the depth of periodontal pocket was measured with William's probe. Regarding to the morphology of bacteria, proportion of cocci, non-motile rod, motile rod and spirochete was measured with a microscope for each week. Regarding to
20 cultivation of microorganisms, the variation ratio dependent upon time was measured for each week. And the following result was obtained.

1. Clinical indices such as plaque indices,
25 gingival indices, the depth of periodontal pocket and

bleeding indices showed significant difference after administration compared to a control group (Table 5-8, fig. 1-4).

2. After administration, the ratio of cocci and non-motile rod was increased, and motile rod and spirochete were reduced (Table 9-12, fig. 5-6).

3. Colony Forming Unit (CFU) of each media was significantly reduced when bacteria was cultivated in aerobic or anaerobic blood agar media (Table 13-15, fig. 7-9).

According to a result of the above test, it is proved that the clinical indices, the variation of bacteria and the concentration of drug in the periodontal pocket shows that the pharmaceutical composition for periodontitis of present invention is very effective for longer than 2 weeks, when it is locally administered.

20 <Table 5> Comparison of plaque indices

group week	Control	Experiment
0	3.00 ± 0.00	3.00 ± 0.00
1	3.00 ± 0.00	2.71 ± 0.46**
2	2.42 ± 0.50*	1.47 ± 0.60**
4	1.66 ± 0.48*	1.33 ± 0.48**

Note : * Significantly different from baseline (0 week)

Significantly different from control group

<Table 6> Comparison of gingival indices

5

group week	Control	Experiment
0	3.00 ± 0.00	3.00 ± 0.00
1	2.71 ± 0.46*	2.23 ± 0.43*#
2	2.28 ± 0.46*	1.47 ± 0.51*#
4	2.00 ± 0.59*	1.33 ± 0.48*#

10

Note : * Significantly different from baseline (0 week)

Significantly different from control group

15

<Table 7> Comparison of pocket depth

group week	Control	Experiment
0	5.85 ± 1.15	5.80 ± 1.12
1	5.42 ± 1.43	4.61 ± 0.58*#
2	5.00 ± 0.00*	4.19 ± 0.67*#
4	4.50 ± 0.78*	3.44 ± 0.85*#

20

Note : * Significantly different from baseline (0 week)

Significantly different from control

25

<Table 8> Comparison of bleeding indices

week	group	Control	Experiment
0		3.00 \pm 0.00	2.87 \pm 0.32
1		2.85 \pm 0.35	2.42 \pm 0.50**
2		2.42 \pm 0.50*	1.90 \pm 0.43**
4		1.50 \pm 0.51*	1.22 \pm 0.42**

Note : * Significantly different from baseline (0 week)

Significantly different from control

<Table 9> Proportion of cocci to total microorganisms
for each week (particular bacteria/ total bacteria \times
100, mean % \pm SD)

week	group	Control	Experiment
0		33.51 \pm 11.86	32.92 \pm 9.14
1		54.49 \pm 12.08*	59.25 \pm 12.14*
2		60.76 \pm 9.81*	60.11 \pm 11.62*
4		66.35 \pm 8.42*	65.01 \pm 10.07*

Note : * Significantly different from baseline (0 week)

<Table 10> Proportion of non-motile rod to total microorganism for each week (mean % \pm SD)

5

group week	Control	Experiment
0	20.47 \pm 4.33	20.00 \pm 6.41
1	19.65 \pm 8.75	21.45 \pm 9.13
2	21.68 \pm 8.93	23.20 \pm 11.24
4	22.96 \pm 9.61	25.68 \pm 9.90

10 Note : * significantly different from baseline (0 week)

<Table 11> Proportion of motile rod to total microorganism for each week (mean% \pm SD)

15

group week	Control	Experiment
0	27.99 \pm 6.49	28.02 \pm 6.43
1	20.01 \pm 5.28	10.11 \pm 7.01*
2	15.21 \pm 8.90	11.87 \pm 7.03*
4	6.61 \pm 4.11*	6.20 \pm 4.43*

20

Note : * Significantly different from baseline (0week)

<Table 12> Proportion of spirochete to total
microorganism for each week (mean% \pm SD)

5

group week	Control	Experiment
0	17.94 \pm 8.12	19.05 \pm 7.19
1	7.51 \pm 7.20*	9.16 \pm 5.37*
2	5.86 \pm 6.46*	4.25 \pm 3.77*
4	4.32 \pm 2.60*	3.13 \pm 3.19*

10 Note : * Significantly different from baseline (0 week)

<Table 13> Comparison of Black-pigmented Bacteroides
(mean CFU % \pm SD)

15

group week	Control	Experiment
0	100.00 \pm 0.00	100.00 \pm 0.00
1	94.31 \pm 37.08	71.80 \pm 16.53**
2	122.30 \pm 48.34*	71.07 \pm 24.50**
4	136.72 \pm 38.04*	90.98 \pm 26.02#

20

Note : * Significantly different from baseline (0 week)

Significantly different from control

25

<Table 14> Comparison of aerobic blood agar plate
(mean CFU % \pm SD)

5

group week	Control	Experiment
0	100.00 \pm 0.00	100.00 \pm 0.00
1	109.21 \pm 13.64	63.31 \pm 43.11**
2	101.41 \pm 19.48	29.18 \pm 17.91**
4	113.75 \pm 23.66	38.34 \pm 18.69**

10 Note : * Significantly different from baseline (0 week)

Significantly different from control

<Table 15> Comparison of Anaerobic blood agar plate
(mean CFU % \pm SD)

group week	Control	Experiment
0	100.00 \pm 0.00	100.00 \pm 0.00
1	100.40 \pm 20.34	73.17 \pm 6.84**
2	92.85 \pm 13.13	65.12 \pm 15.17**
4	108.41 \pm 13.47	67.48 \pm 16.65**

Note : * Significantly different from baseline (0 week)

Significantly different from control

What is claimed is :

1. The locally administrable, biodegradable and sustained-release pharmaceutical composition for
5 periodontitis characterized in comprising microspheres containing an active substance and water-soluble polymer in the form of film or strip.
2. The locally administrable, biodegradable and
10 sustained-release pharmaceutical composition for periodontitis characterized that the film or strip of Claim 1 is coated by aqueous solution of cation salt.
3. The locally administrable, biodegradable and
15 sustained-release pharmaceutical composition according to Claim 1 or Claim 2, characterized that the active substance is selected from the group of the following materials; ampicillin, amoxicillin, erythromycin, tetracycline, minocycline, oxytetracycline,
20 doxycyclin, metronidazole, bacitracin, kitasamycin, spiramycin, ornidazole, and their salts as antibiotics, lidocaine, procaine, dibucaine, and benzocaine as local anesthetics, and diclofenac, flubiprofen, ibuprofen, ketoprofen, aspirin, mefenamic acid and acetaminophen
25 as antiinflammatory analgesics, and dexamethasone,

triamcinolone acetone, hydrocortisone, epihydrocortisone as steroid hormones.

4. The locally administrable, biodegradable and
5 sustained-release pharmaceutical composition according
to Claim 1 or Claim 2, characterized that the
biodegradable polymer composing microspheres is
selected from the group of polyglycolic acid(PGA),
polylactic acid(PLA) and polylactic-glycolic acid(PLGA)
10 whose average molecular weight is in the range of
4,000 to 50,000.

5. The locally administrable, biodegradable and
sustained-release pharmaceutical composition, according
15 to Claim 1 or Claim 2 characterized that the
biodegradable microspheres contains physiologically
active substance more than 20 weight %, and release the
physiologically active substance for 1 to 3 weeks
continuously.

20

6. The locally administrable, biodegradable and
sustained-release pharmaceutical composition according
to Claim 1 or Claim 2, the water-soluble polymer
contains the polysaccharides such as pectin,
25 carrageenan, gelatin, sodium alginate or chitosan.

7. The locally administrable, biodegradable and sustained-release pharmaceutical composition according to Claim 2, characterized that the cation salt solution
5 contains calcium chloride, magnesium chloride, or barium chloride.

8. The process for preparation of locally administrable, biodegradable and sustained-release
10 pharmaceutical composition for periodontitis characterized in comprising 1) the step of making microspheres containing physiologically active substance by dissolving biodegradable polymer in the solvent and suspending the active substance into the
15 solution followed by emulsifying the suspended solution in the aqueous solution containing the surfactant, 2) the step of making hydrogel by mixing the microspheres and water-soluble polymer, and then adding distilled water and 3) the step of making films or strips from
20 the hydrogel.

9. The process for preparation of locally administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis
25 characterized in comprising 1) the step of making

microspheres containing physiologically active substance by dissolving biodegradable polymer in the solvent and suspending the active substance into the solution, followed by emulsifying the suspended solution in the aqueous solution containing the surfactant, 2) the step of making hydrogel by mixing the microspheres and polysaccharides polymer, and then adding distilled water, 3) the step of making films or strips from the hydrogel, and 4) the step of coating and drying utilizing spray-coating method to the films or strips with aqueous cation salt solution.

10. The process for preparation of locally administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis according to Claim 8 or Claim 9, characterized that diameter of physiologically active substance particle is below $5\mu\text{m}$, the surfactant is polyvinyl alcohol, the concentration of the surfactant is 1 to 15 weight %, the temperature of the aqueous solution is below 10°C , and the surfactant in the diluted solution is 0.1 to 1 weight %.

11. The process for preparation of locally administrable, biodegradable and sustained-release

pharmaceutical composition for periodontitis according to Claim 8 or Claim 9, characterized that mixing ratio of the water-soluble polymer and microspheres is 5 : 95 to 50 : 50.

5

12. The process for preparation of locally administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis according to Claim 8 or Claim 9, characterized that
10 concentration of the water-soluble polymer or polysaccharides in the above hydrogel is 1 to 20 weight %.

13. The process for preparation of locally
15 administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis according to Claim 9, characterized that cation salt contains calcium chloride, magnesium chloride, or barium chloride.

20

14. The process for preparation of locally administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis according to Claim 9, characterized that concentration
25 of the cation aqueous solution is 2 to 5 weight %.

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Fig.1 Plaque Indices

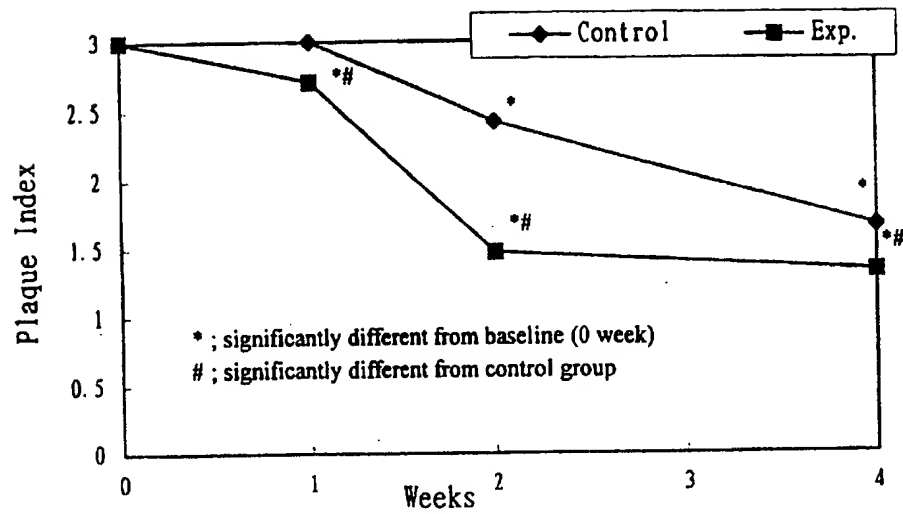
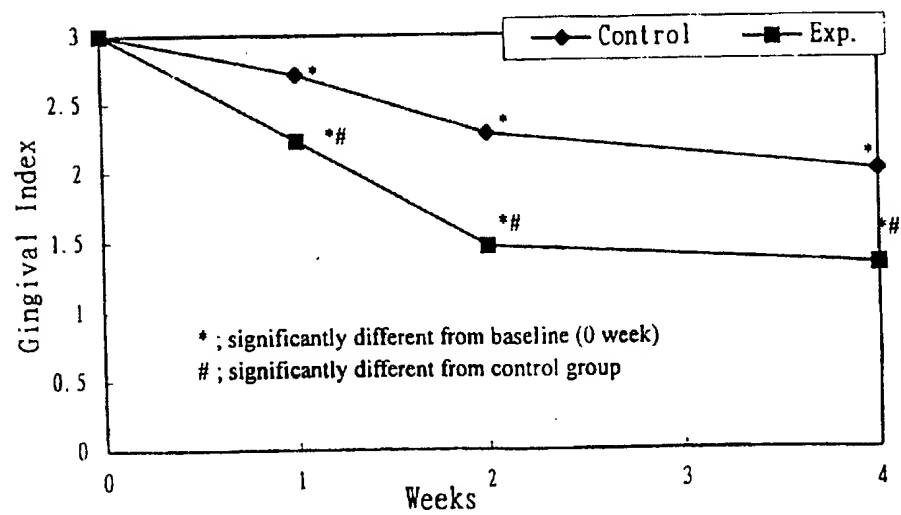


Fig.2 Gingival Indices



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Fig. 3 Pocket Depth

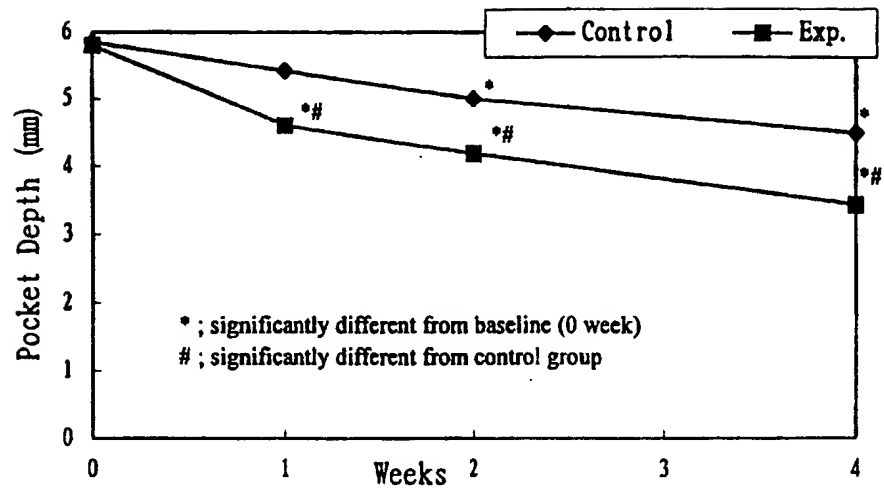
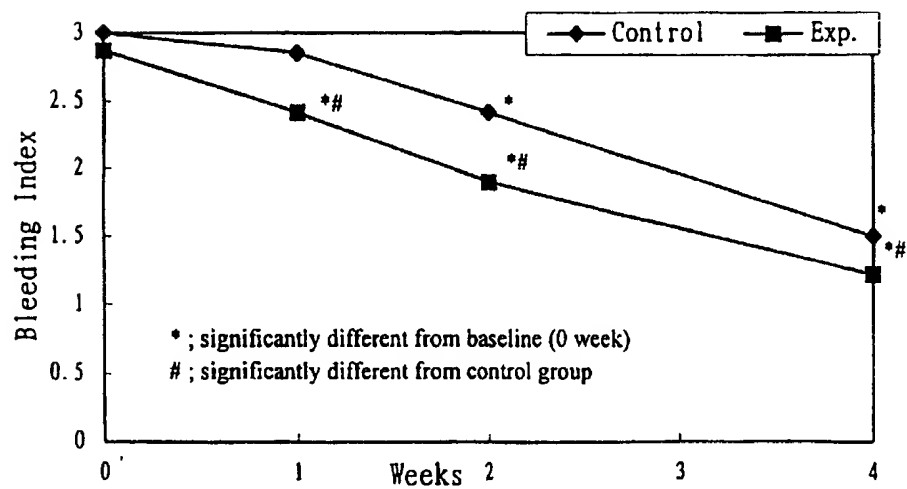


Fig. 4 Bleeding Indices



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Fig. 5 Control

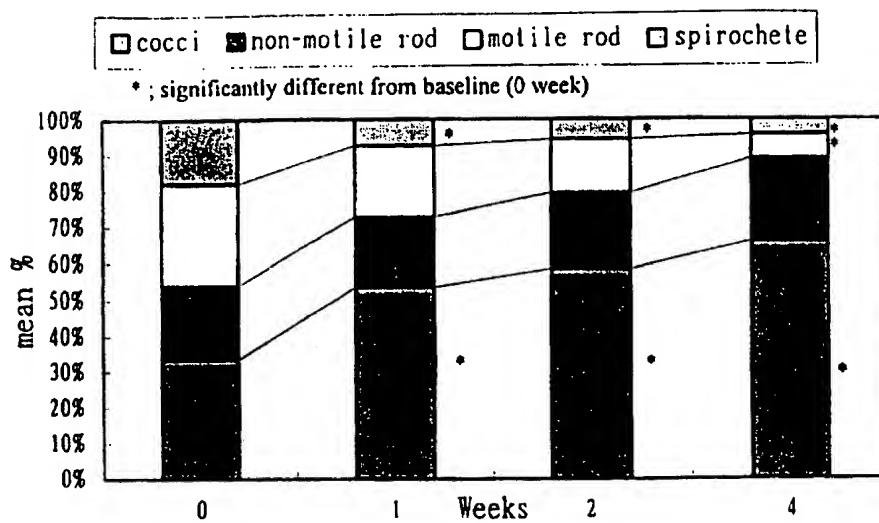
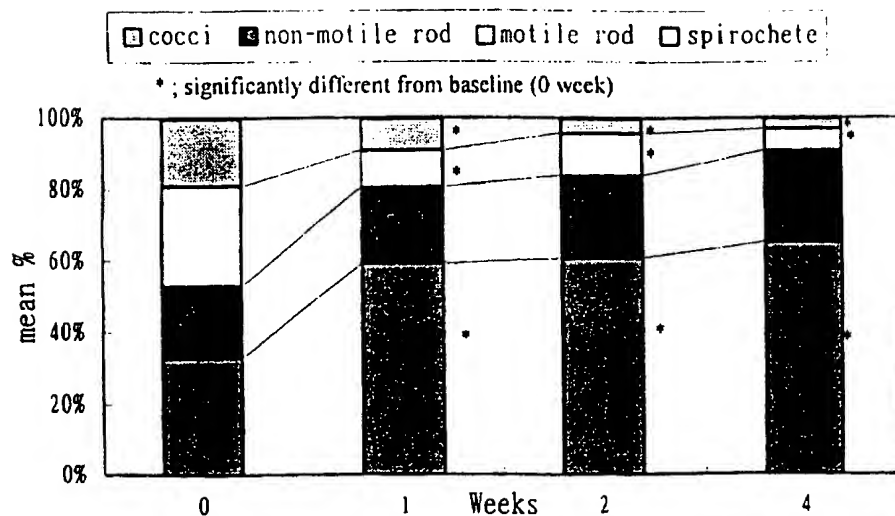


Fig. 6 Experiment



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Fig.7 Black-pigmented Bacteroides

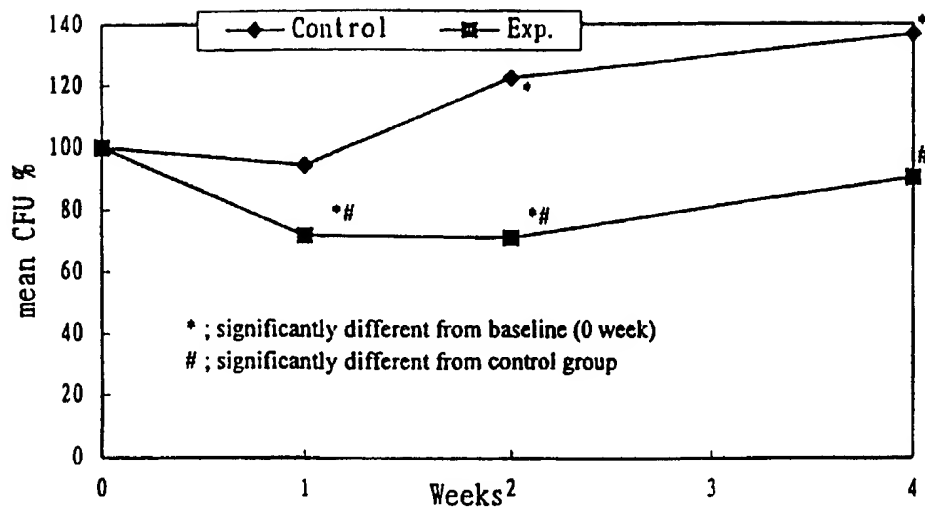
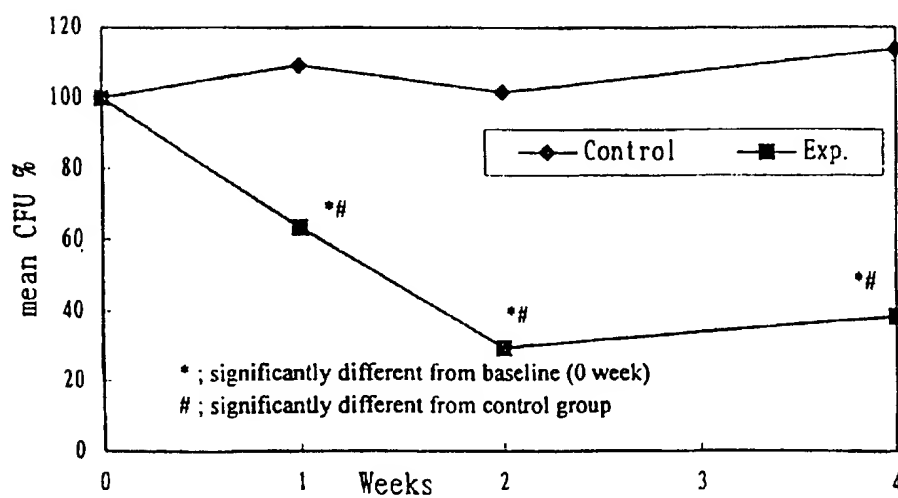
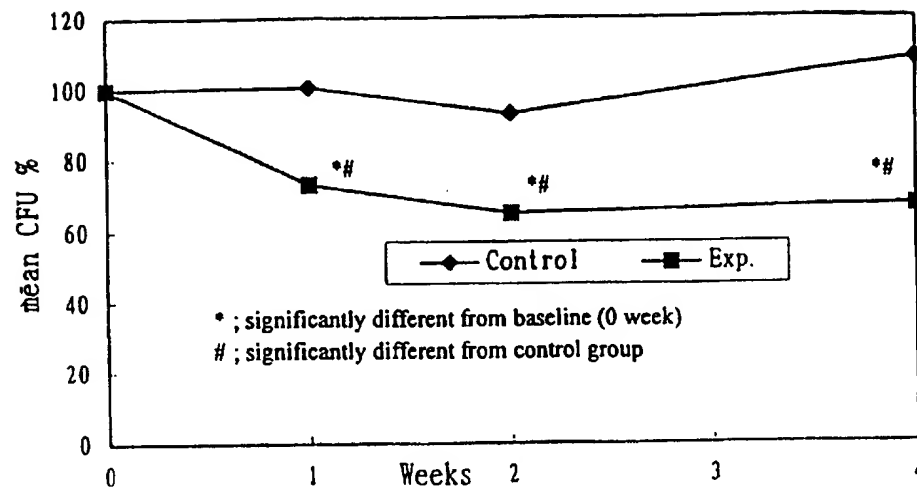


Fig.8 Aerobic blood agar plate



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Fig.9 Anaerobic blood agar plate



INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 97/00093

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: A 61 K 9/22, 9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: A 61 K 9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 933 182 A (HIGASHI K. et al.) 12 June 1990 (12.06.90), abstract; claims 1,3; example 1; column 3, lines 28-42; column 4, line 54 - column 5, line 9; column 5, lines 19-30 (cited in the application).	1,3,4,6
X	EP 0 244 118 A1 (PHARMETRIX CORPORATION) 04 November 1987 (04.11.87), claims 1-4,6-10; example 3; page 5, line 1 - page 6, line 5; page 7, line 27 - page 9, line 18; page 13, line 14 - page 14, line 18 (cited in the application).	1,3,8,10-12
X	EP 0 451 390 A1 (PHARMETRIX CORPORATION) 16 October 1991 (16.10.91), abstract; claims 1-3,6-8; page 6, lines 37-58; page 9, lines 3-15.	1,3-5
X	WO 90/00 048 A1 (TEMPLE UNIVERSITY OF THE COMMON-WEALTH SYSTEM OF HIGHER EDUCATION) 11 January 1990 (11.01.90), claims 1,2,4-6,8-10; example 1.	1,3

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Name and mailing address of the ISA/ AT
 AUSTRIAN PATENT OFFICE
 Kohlmarkt 8-10
 A-1014 Vienna
 Facsimile No. 1/53424/535

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INTERNATIONAL SEARCH REPORT
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Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche		Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A	4933182	12-06-90	AU A1 70616/87	01-10-87
			AU B2 618932	16-01-92
			CA A1 1300515	12-05-92
			DE C0 3775805	20-02-92
			EP A1 241178	14-10-87
			EP B1 241178	08-01-92
			JP A2 62223112	01-10-87
			JP B4 5084282	01-12-93
EP A1	244118	04-11-87	AU A1 72112/87	05-11-87
			AU B2 614061	22-08-91
			CA A1 1309345	27-10-92
			DE C0 3787829	25-11-92
			DE T2 3787829	11-05-94
			DK A0 2192/87	29-04-87
			DK A 2192/87	30-10-87
			EP B1 244118	20-10-92
			JP A2 63027422	05-02-88
			NO A0 871774	26-04-87
			NO A 871774	30-10-87
			NO B 177125	18-04-95
			NO C 177125	21-07-95
			NZ A 219928	29-11-88
			US A 4780320	25-10-88
			US A 4919939	24-04-90
EP A1	451390	16-10-91	AU A1 52166/90	03-10-91
			CA A0 2012665	21-09-91
			AU B2 629316	01-10-92
WO A1	9000048	11-01-90	AU A1 38518/89	23-01-90
			AU B2 613298	25-07-91
			DK A 515/90	27-02-90
			DK A0 515/90	27-02-90
			EP A1 393164	24-10-90
			EP A4 393164	03-07-91
			JP T2 3501485	04-04-91
			NO A0 900927	27-02-90
			NO A 900927	23-04-90
			NZ A 229356	26-02-91
			PT A 900994	29-12-89
			US A 4917892	17-04-90
			ZA A 8904308	28-02-90

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